Prevalence of Hepatitis B in HIV infected persons: Choice of antiretroviral therapy regimen and implications for screening.

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DECLARATION

MPH (General) Mini-Dissertation

I, Derval Reidy Student No. RDYDER002 hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background: Limited data and few studies have shown the prevalence of Hepatitis B in the HIV infected population in South Africa, whether these patients are on appropriate antiretroviral therapy and the effect of Hepatitis B on liver function in co-infected persons.

Objectives: The objectives of this study were to determine the prevalence of Hepatitis B surface antigemia (HBsAg) in healthy HIV positive persons screened for a vaccine trial and the proportion of those eligible for antiretroviral therapy that were receiving optimal anti-viral treatment, namely tenofovir and/or lamivudine. The relationship between Hepatitis B carriage and liver function was also determined in co-infected persons as measured by liver function tests.

Methods: A cross sectional study was conducted from 30th August 2011 to 24th April 2013 to determine the prevalence of HIV/HBV co-infection in persons attending a clinical trial site in an urban clinical trials unit of Cape Town. Participants self-presented to the clinic and once consented were enrolled into the study and provided blood for HIV confirmatory test, Hepatitis B s Ag, CD4, VL, full blood count, liver function and renal function tests.

Results: 638 participants were enrolled into this cross sectional study. 24 (3.8%) were Hepatitis B s Ag positive, which was lower than expected. Of the 24 HIV/HBV co-infected participants, 19 (79.2%) were on antiretroviral therapy, 14 (73.7%) of these were on a tenofovir/lamivudine regimen the remaining 5 (26.3%) were not on a tenofovir regimen. Five of the co-infected participants were not on ARVs because their CD4 count was above the recommended South African guidelines for treatment i.e. greater than 350 10^6/l. Male participants were three times more likely to be HBsAg positive. Elevated Alanine aminotransferase (ALT) and Aspartate Aminotransferase (AST) were associated with HBsAg seropositivity.

Conclusion: This study showed a lower HIV/HBV co-infection prevalence rate than reported from other locations in South Africa suggesting geographical variability. Appropriate guidelines are required to ensure that co-infected patients are identified and treated with the most appropriate anti-retroviral regimens. Screening for HBV is also recommended in HIV-infected cohorts.

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Part A:

Prevalence of Hepatitis B in HIV infected persons: Choice of antiretroviral therapy regimen and implications for screening.

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1. PROTOCOL SUMMARY:

Title	Prevalence of Hepatitis B in HIV infected persons: Choice of antiretroviral therapy regimen and implications for screening.
Study design	Observational cross sectional study
Population	All HIV positive participants recruited for a TB vaccine study attending a clinic in Khayeltisha, Cape Town.
Site	Khayelitsha, Cape Town.
Study objectives	The study objectives will be to ascertain: 1. The prevalence of Hepatitis B surface antigemia in HIV positive persons screened for a vaccine trial. 2. The percentage of those eligible for ART that are receiving optimal anti-viral treatment such as tenofovir and/or lamivudine. 3. The relationship between Hepatitis B carriage and liver abnormalities determined by Liver Function Tests in co-infected persons.
Methods	A sample of 638 HIV positive participants recruited for a TB vaccine study from 30th August 2011 to 24th April 2013. All participants had their HIV status confirmed and bloods taken for hepatitis B surface antigen, liver function, viral loads and CD4 tests as part of the vaccine trial. The ART status of every participant was also ascertained.

2. Background Information and Rationale

HIV and Hepatitis B (HBV) represent two significant global health problems. Both are preventable viral infections which are on the increase. Currently there are an estimated 50 million people living with HIV [1] and 400 million people living with Hepatitis B [2]. An estimated 1.2 million people die annually from complications associated with chronic Hepatitis B [3]. Chronic HBV is endemic in Sub-Saharan Africa with prevalence rates varying from 0.3 to 15 % [4]. HIV rates in Sub-Saharan Africa are estimated to be 4.9% amongst 15-49 year olds in 2011 [5]. In 2011, HIV prevalence rates in South Africa were over 10% [6]. Many of the countries where Hepatitis B is endemic also have a high burden of HIV leading to an increase in HIV/HBV co-infection rates [2]. Co-infection leads to increased liver morbidity and mortality, increased hepatitis B viral replication and hepatotoxicity induced by the combination of HBV and anti-retroviral medication [2]. Also, there is evidence to suggest that HIV accelerates the progression of HBV liver disease [7].

Globally there is very little data on HIV/HBV co-infection rates, particularly in countries with high prevalence of chronic Hepatitis B. Estimated co-infection rates in Sub-Saharan Africa are 15% but vary greatly depending on the country [7]. Co-infection prevalence rates in South Africa are currently unknown. Different studies conducted in urban clinics in Johannesburg have estimated a 5% HBsAg positivity rates in HIV positive patients [8] and up to 17% in an industrial clinic setting [9].

There is an increased need to screen for HBV prior to commencement of anti-retroviral (ARV) therapy and to screen patients currently on ARVs to ensure they are receiving optimal treatment as some antiretrovirals are also effective against HBV. There is an obligation to increase community and health care professional awareness surrounding co-infection to prevent further spread of the virus and to ensure optimal care. The anti-retroviral treatment

programme has reversed the decline in life expectancy and it has increased from 48 years pre-ARVs to 54.9 years in 2011 in South Africa [6]. As the HIV and Hepatitis B epidemics progress we need to understand the impact of HBV on liver function in co-infected persons.

The aim of this study is to determine the HIV/HBV co-infection rate amongst HIV-infected participants of a TB vaccine trial and to determine if these co-infected participants are receiving optimal anti-retroviral therapy.

3. Literature Review

The modes of transmission for both these viral infections are contact with blood or other body fluids of an infected person i.e. through unprotected sexual contact, perinatally from mother to child, or via infected blood in needle stick injuries or use of infected needles by injecting drug users. However, Hepatitis B is 50 to 100 times more infectious than HIV [10]. Hepatitis B can be a serious viral infection which affects the liver. The presence of HBsAg for a minimum of six months indicates chronic infection. Ma [11] estimates that HBV is the fourth most common cause of cancer death amongst Asian Americans. Approximately 20% of liver cirrhosis amongst black Africans is secondary to HBV [12].

Patterns of transmission differ between developed and developing countries. In developed countries acquisition of Hepatitis B mainly occurs in adulthood in high risk groups through intravenous drug use or sexual exposure. In contrast, acquisition of Hepatitis B in developing countries is predominantly perinatal (from mother to infant at birth) or horizontal (i.e. that occurring without apparent parenteral, sexual or perinatal exposure)[13]. The predominant mode of HBV transmission in the world is perinatal [1]. A pregnant woman who is Hepatitis B e antigen positive has a 90% probability of transmitting HBV to her new born child. Twenty five percent of these children will die in adulthood from chronic liver disease or liver cancer [1]. Little is known about HBV prevalence in the general population in South Africa.

Chronic HBV is the cause of 1.2 million deaths per year worldwide [3]. Sub-Saharan Africa has the second highest HBV prevalence rates following Asia [14]. However, only a small proportion of patients with chronic HBV are placed on appropriate antiviral treatment resulting in an increased risk of liver cancer [3].

The patterns of transmission for HIV acquisition also differ between developed and developing countries. In developed countries HIV incidence is mainly in high risk adult groups – men who have sex with men, sex workers and intravenous drug users. However, sexual acquisition is increasing in heterosexual groups. In developing countries and in particular sub-Saharan Africa, HIV is predominantly perinatal or horizontal transmission [13]. The majority of the data regarding co-infection comes from developed countries and do not reflect transmission patterns in developing countries.

HIV is a retrovirus which attacks the immune system, causing AIDS (Acquired Immune Deficiency Syndrome) if untreated. Although not curable, HIV infection can be well controlled by anti-retroviral medications. Since the introduction of anti-retrovirals in South Africa, there has been a marked decrease in HIV related deaths.

The South African Clinicians Society [13] has warned that HIV-Hepatitis B co-infected patients are at increased risk of morbidity and mortality. The World Health Organization's clinical protocol for Management of HBV and HIV co-infection highlights that patients receiving anti-retroviral treatment have an increased risk of hepatotoxicity and that interruption in treatment can cause hepatic flare ups. HIV has a significant impact on HBV, it increases the risk of liver cirrhosis and end stage liver disease in co-infected individuals. The risk of liver related mortality is 2-3 times higher in co-infected individuals compared to mono-infected patients [14] [15]. Also, HIV co-infection is associated with more frequent flares of hepatic transaminases. Immune reconstitution inflammatory syndrome (IRIS) can

occur once a patient starts on Antiretrovirals (ART). Interruption of HIV/HBV treatment can result in hepatic flare ups and or the development of resistance to treatment [16].

Both the World Health Organization and the South African HIV Clinician's society recommend early screening for Hepatitis B in HIV infected patients. This should be conducted at the time of diagnosis. Despite these recommendations, the National Department of Health guidelines no longer recommend Hepatitis B testing in HIV infected adults. Hepatitis B screening (HBsAg) is advised in the 2010 guidelines in patients starting nevirapine but only in patients with a raised ALT. Prior to that screening for HBsAg was not included in the guidelines.

The ARVs lamivudine and tenofovir are part of the effective treatment of both HIV and HBV and both are available in South Africa. Tenofovir was approved for the treatment of HBV in 2008 [7] and became available in South Africa in 2010. Lamivudine has a poor resistance profile and drug resistance mutations commonly occur after two to three years of use [18]. In addition HBV flare-ups often occur if HBV treatment is stopped [19]. Tenofovir has a much better resistance profile and fewer side effects than lamivudine and is now part of first line therapy for HIV. Because tenofovir is part of the first line regimen for HIV and is the preferred treatment option for both HIV and HBV, it was argued that HBV screening was no longer required.

HBV vaccination has been routinely available as part of the Expanded Programme on Immunization (EPI) in South Africa since 1995 [12]. However, persons born before 1995 are susceptible to HBV. All HIV-infected persons born prior to this year should therefore be screened for HBV and vaccination should be provided if not infected or if they missed part of

their vaccination doses. In persons who are not co-infected with HIV, tenofovir may provide pre-exposure prophylaxis against HBV [20].

There is an urgent need to determine the prevalence of HBV infection in HIV-infected persons, the proportion of HIV/HBV co-infected persons on appropriate ARVs, the effect of HBV on the liver in co-infected persons and early detection of liver complications. This study will address these key issues.

4. Study Aims and Objectives

4.1 Research Questions

What is the prevalence of HBV surface antigemia in a healthy HIV infected adult cohort of participants screened for a Tuberculosis vaccine trial? What percentage of these participants are on appropriate anti-retroviral treatments? Do co-infected participants with HIV/HBV have abnormal liver function tests?

4.2 Study Aims

This study aims to determine the Hepatitis B prevalence rates in a healthy HIV infected adult cohort of participants screened for a Tuberculosis vaccine trial and if these participants are on appropriate anti-retroviral treatment.

4.3 Objectives

The study objectives will be to ascertain:

4.3.1 What is the prevalence of Hepatitis B surface antigemia in HIV positive persons screened for a TB vaccine trial?

4.3.2 What percentage of those co-infected participants are receiving appropriate optimal therapy such as tenofovir/lamivudine or emtricabine?

4.3.3 What is the relationship between Hepatitis B co-infection and abnormality in Liver Function Tests?

5. Methods

5.1 Study design and setting

This will be an observational cross sectional study using data from a pre-existing TB vaccine trial. All HIV-infected participants aged 18-50 years of age screened for the TB vaccine trial at a clinical trials unit in Khayelitsha from 30 August 2011 to 24 April 2013 will be included in this cohort. Khayelitsha is an urban township on the outskirts of Cape Town. Adults aged 15-54 years of age comprise 66.7 % of the population. Half of all adults are unemployed and of those employed, 80% earn less than R1600 per month [18].

5.2 Study Population

The study population will include all HIV positive participants screened for a TB vaccine trial and identified as HIV-infected as part of the screening process for the vaccine trial.

5.2.1 Eligibility criteria

The following participants will be included in this cohort:

Inclusion Criteria:

- Confirmed HIV ELISA positive
- Aged 18-50 years on day of screening

Exclusion Criteria:

- HIV negative.
- No blood results available.

For full inclusion and exclusion criteria for the TB vaccine trial refer to Appendix 1.

5.2.2 Method of sampling

All HIV infected participants enrolled in the TB vaccine trial over a twenty month period from 30 Aug 2011 to 24 April 2013 will be included. In order to determine the proportion of co-infected participants on the appropriate ARVs a sub-sample will include all co-infected (HIV/HBV) participants of the TB vaccine trial.

5.2.3 Sample size

If the expected prevalence of co-infection is 4%, a sample of 638 HIV-infected participants will provide an estimate with a 1.25% margin of error. Calculating the confidence interval for a proportion, the margin of error will be 1.25%. In the sub-sample of co-infected patients a sample size of 638 will have a 95% confidence interval of 2.75 to 5.25%

5.3 Study Procedures

All HIV-infected participants screened for the TB vaccine trial will be eligible for this study. Participants with confirmed HIV laboratory results will be entered into the study. Information will be retrieved from information gathered from the TB vaccine trial. This study will not require any additional laboratory tests or procedures or study visits.

5.4 Study endpoints

- Prevalence rate of co-infected HIV/HBV participants.

- Proportion of co-infected participants on appropriate ARVs
- Proportion of co-infected participants with abnormal liver function tests.

5.5 Feasibility

This study will use data from the TB vaccine trial conducted in Khayelitsha. No new data will be collected. No additional staff will be required for this study.

6. Measurement and Field Management

6.1 Instruments

All data will be obtained from the TB vaccine study. Basic demographic details, contact information and date of first screening visit will be collected from the clinic folder and completed on a study log sheet.

Information will be retrieved from the TB study data base – age, ARV status, if on ARV which ARVs, consumption of alcohol, smoking status, laboratory results – confirmation of HIV and HBV status, CD4, viral load, liver function tests.

Regarding alcohol consumption, the following questions will be asked to ascertain the amount of alcohol participants consumed (A unit is defined as 1 drink = half large beer, glass of wine, shot of spirit))

Regarding alcohol consumption, are you a Non-drinker; Currently consume alcohol;

Ex-drinker > 1 year or an Ex-drinker < 1 year.

If current drinker, how many drinks have you consumed in the last week?

0 units; 1-7 units or >7 units

6.2 Variables

The dependent variable will be HIV/HBV positive. Independent variables will include age at time of screening, sex, ARV status, consumption of alcohol, smoking status and laboratory results.

6.2.1 Table 1. Variables Table

Variable	Scale	Options
Dependent variable:		
HIV ELISA confirmation	Binary	Yes=1 No=0
Hepatitis B s Antigen confirmation	Binary	Yes=1 No=0
Independent variables:		
Age of participant	Continuous	18 – 50 years
Sex	Binary	Male=1 Female=0
ARV status	Binary	Yes=1 No=0
Types of ARVs	Nominal	Tenofovir/lamivudine, emtricabine/non-nucleoside reverse transcriptase inhibitor.
Alcohol consumption	Binary	Yes=1 No=0
Laboratory Results:		
CD4	Continuous	Range: 500 - 2010X 10^6/l
HIV Viral Load	Continuous	Range: <50-500,000 copies/ml
Bilirubin	Continuous	Range: 0-21 µmol/l
Alanine Transferase	Continuous	Range: 5-40 U/L
Aspartate Transaminase	Continuous	Range: 5-40 U/L
Alkaline Phosphatase	Continuous	Range: 40-120 U/L
Gamma GT	Continuous	Range: 0-35 U/L

6.3 Validity and reliability

Quality control measures will be taken to ensure that all study procedures were retrieved according to the protocol. Data capturing sheets will be marked with participant specific study numbers and stored to ensure easy retrieval in the case of queries. All data is checked against source documentation to ensure that the correct information has been entered.

For this study all data will be checked through a computer based listings of variables to assess for any inconsistencies or missing values in the dataset. Categorical data will be checked for correct coding and missing variables. Numerical variables will be checked for plausible ranges and missing values. Where "stem and branch" questions are used, they will be cross-checked for any inconsistencies by comparing the answers to each of those questions. Any inconsistencies and or missing values identified will be queried and tracked back to the source documents to help investigate and resolve the problem using the study number.

7. Statistical and Data Management and Analysis

7.1 Data management and Statistical analysis

Numerical data will be summarised using means and standard deviations or medians and interquartile ranges for the overall cohort depending on the distribution of data. For binary outcomes, proportions with 95% confidence intervals will be presented. Chi-squared and Fisher's Exact tests will be used in univariate analysis. Odds ratios will be calculated and reported with 95% confidence intervals.

A multivariate logistic regression model will explore associations between independent risk factors (age, gender, smoking status, alcohol consumption, ARV status) and the dependent variable, positive HIV and HBV status. Further variables are described in the Table 1 Variables Table. Analysis will also be conducted to assess and adjust for possible confounding by variables such as age and gender. All data will be analysed using Stata version 12.

8. Ethics

Full ethics approval has been obtained for the vaccine trial "A Phase 2, Proof of concept, Randomized, Double-blind, Placebo-controlled Study to evaluate the Protective efficacy against TB disease, safety and immunogenicity of MVA85A/AERAS-485 in Healthy, HIV-infected Adults", ethics ref 001/2010 (Appendix 1).

All information which will be used for this study has been approved as part of the above TB vaccine study. All participants have signed full informed consent to be part of the TB vaccine trial and this study will not require any additional information from the participants.

Written informed consent was obtained from all participants within the confines of the TB vaccine trial. Full informed consent has been obtained in the preferred language of the participant which will be Xhosa or English which are the main languages spoken locally. Participation is voluntary and participants may withdraw from the study at any time if they choose to without having to give a reason.

The study is conducted according to the principles of Good Clinical Practice and followed ICH-GCP and SA GCP guidelines.

9. Stakeholders and Reporting

The results of this study will be disseminated to all relevant stakeholders including the Western Cape Provincial Health Department, City of Cape Town Health and staff working at clinic where the trial was conducted. In addition feedback will be given to local community representatives. The study findings will be submitted for publication to a peer-reviewed journal of public health (South African Medical journal) within a year of study completion. In addition the findings may be presented at both a national and international conference.

10. Strengths and Limitations

The major strengths of this study are that it will ascertain HIV/HBV co-infection rates within this population. This study will provide critical information on current prevalence rates, if participants are on appropriate ARVs given their Hepatitis B status and if co-infected participants have abnormal liver function tests.

11. Logistics

11.1 Budget

No additional budget is required for this study and any expenses incurred will be covered by the vaccine trial.

11.2 Timeline for study completion

Year	**2013**							
Month	M	J	J	A	S	O	N	D
Ethics Submission	■							
Database - develop		■						
Data collection			■					
Data entry				■				
Data analysis					■			
Dissemination						■	■	■
Write-up and publish						■	■	■

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Part B: Structured Literature Review

1. Abbreviations and acronyms

AIDS	Acquired Immune Deficiency Virus
ALT	Alanine aminotransferase
ART	Anti-Retroviral
AST	Aspartate aminotransferase
CD 4	CD4+ lymphocytes
EPI	Expanded Program on Immunization
HBV	Hepatitis B Virus
HBeAg	Hepatitis B e Antigen
HBsAg	Hepatitis B s Antigen
HIV	Human Immunodeficiency Virus
WHO	World Health Organization

2. Introduction and Objective of Literature Review

This literature review focuses on Human Immunodeficiency Virus (HIV) and Hepatitis B (HBV) co-infection including the global epidemiology of these diseases, the epidemiology in sub-Saharan African and more specifically in South Africa. Particular attention is also paid to the clinical diagnosis, aetiology and prognosis of co-infection. A review of the global guidelines for the treatment of co-infection from the World Health Organization and from the South African Clinician's Society is included. A review of studies based in South Africa on co-infection is also conducted.

The objectives of this literature review are:

- To describe studies on the prevalence of HIV, Hepatitis B and co-infection rates, globally and in South Africa.
- To describe guidelines for co-infected patients in terms of anti-retroviral (ARV) treatment as well as studies of current practices.
- To describe studies of liver function of co-infected patients.

3. Search Strategy

The following strategy was used to inform this literature review:

Strategy: Search engines were used to search for combinations of the listed search items as stated below. Relevant articles suggested by search engines were included. References in articles were checked so as to identify any other relevant studies. Quantitative studies were included. Articles describing systematic review, case reports, observational studies, case series and trials were included. The initial search

strategy focused on co-infection from Sub-Saharan Africa but due to the limited nature of research from Africa, research from the developed world was also included. World Health Organization treatment guidelines, South African Clinician's society treatment guidelines, WHO reports, UNAIDS reports were sourced from their websites for information regarding current prevalence rates and standard of care.

Search Terms:

- HIV and Hepatitis B co-infection
- HIV in Sub-Saharan Africa/South Africa
- Hepatitis B in Sub-Saharan Africa/South Africa
- HIV and Hepatitis B co-infection in Sub-Saharan Africa/South Africa
- Recommended ART treatment in co-infected HIV and Hepatitis B
- HIV and Hepatitis B and abnormal liver function as determined by liver function tests.

Search Engines: Pubmed, Google, Google Scholar, Science Direct, Medline.

4. Summary of Literature Review

4.1 HIV

Currently there are an estimated 50 million people living with HIV[1]. The African continent carries the bulk of infection and HIV prevalence in sub-Saharan Africa in 2011 was estimated to be 4.9% amongst 15-49 year olds [2].

South Africa has one of the highest rates of HIV infection in the world. In 2011, 10.6% of the population were infected with HIV and 16.6% of the adult population aged 15-49 were HIV positive [3].

HIV is a retrovirus which attacks the immune system, causing AIDS (Acquired Immune Deficiency Syndrome) if left untreated. Although not curable, infection can be well controlled by taking anti-retroviral medications. The success of anti-retroviral

treatment has reversed life expectancy from 48.0 years pre-ARVs to current life expectancy rates of 54.9 years in South Africa (Statistics South Africa, 2011) [3]. However, because of the decreased mortality due to ARVs the prevalence of HIV is increasing and HIV continues to be one of the leading infectious diseases within sub-Saharan Africa.

4.2 Hepatitis B (HBV)

It is estimated that two billion people worldwide have been infected with Hepatitis B (HBV) and more than 240 million people are living with chronic HBV [1]. An estimated 1.2 million people die annually from complications associated with chronic HBV [4]. Chronic HBV is endemic in many parts of Sub-Saharan Africa with prevalence rates varying from 0.3 to 15.0 % [5]. HBV endemicity is defined as a population prevalence greater than 8% [6].

It has been estimated that carrier rates of HBV range from 9.6% in South Africa to 20.6% in the Democratic Republic of the Congo [7]. Even within South Africa, studies have shown marked differences in prevalence rates between rural and urban settings. Kew [8] reported a HBV prevalence rate of 15.5% from the Eastern Cape compared with 1.3% from Soweto. Black ethnic groups tend to have a higher HBV prevalence compared to other racial groups on the continent [9].

Hepatitis B can be a serious viral infection which affects the liver. The presence of HBsAg indicates HBV infection and the presence of HBsAg for a minimum of six months indicates chronic infection. There are two phases of illness an acute phase and chronic phase. The acute phase is characterized by loss of appetite, tiredness, diarrhoea, vomiting and jaundice. Acute hepatitis is often self-limiting and is usually followed by non-replicative infection phase [10]. In fact, more than 90% of adults

develop a broad immune response that eliminates replicating HBV DNA from blood and leads to protection against HBsAg [11]. Following acute infection, the risk of developing chronic infection varies inversely with age: 90% for perinatal infection, 25-30% for infection at age 1-5 years and less than 10% for adults [12]. Patients who develop chronic HBV infection may often be asymptomatic but the infection can lead to liver cirrhosis, liver cancer and death, with an estimated 1 million people dying annually from HBV related disease [1]. Ma [13] estimates that HBV is the fourth most common cause of cancer death amongst Asian Americans. Approximately 20% of liver cirrhosis amongst black Africans is secondary to HBV [8].

The main mode of acquisition of HBV in sub-Saharan Africa is horizontal transmission, with the majority of children between the age of six months and 5 years becoming infected through close contacts within households [14]. These children become chronic carriers of HBV and can transmit it in adulthood the same way as HIV [9].

Hepatitis B is a preventable disease. HBV vaccination has been routinely available as part of the Expanded Programme on Immunization (EPI) in South Africa since 1995, given at 6, 10 and 14 weeks of age [8] and has been rolled out in many other African countries between 1990 and 2001 [9]. Hepatitis B vaccine has a 95% efficacy rate and is the first vaccine against a major human cancer [1]. However, within South Africa, persons born before 1995 are susceptible to HBV. All HIV-infected persons should therefore be screened for HBV and vaccination provided if not immune or if they missed vaccination.

4.3 Co-infection

Globally there is very little data on HIV/HBV co-infection rates, particularly in countries with a high prevalence of chronic hepatitis. It is estimated that approximately 10% of people living with HIV worldwide are also co-infected with HBV [15]. Studies from the developed world show that HBV infection is higher in HIV infected individuals compared to uninfected individuals [9]. A study conducted in an urban government clinic in South Africa showed that a HIV infected person was five times more likely to be infected with HBV compared to a HIV negative person [16]. Estimated co-infection rates in Sub-Saharan Africa are approximately 15.0% but can vary greatly between countries [17]. Co-infection prevalence rates in South Africa are currently unknown. Studies conducted in an urban clinic in Johannesburg estimated a 5.0% HBsAg positivity rates in HIV positive patients compared to 17.0 % in an industrial clinic setting [16].

The South African HIV Clinicians Society [14] warns that HIV-HBV co-infected patients are at increased risk of morbidity and mortality. This may be due to increased HBV viral replication and hepatotoxicity induced by the combination of HBV and anti-retroviral medication [6]. There is also evidence to suggest that HIV accelerates the progress of HBV liver disease [17]. HIV positive patients with low CD4 counts are at increased risk for liver related mortality and reactivation of Hepatitis B in patients with developed immunity [18], [19]. Most of the literature suggests that HIV plays a role in HBV disease progression [1]. However, there is no evidence to suggest that HBV promotes HIV disease progression [20]. The World Health Organization's clinical protocol for Management of HBV and HIV co-infection highlights that patients receiving anti-retroviral treatment have an increased risk of hepatotoxicity and that interruption in treatment can cause hepatic flare ups.

HIV-infected patients exposed to HBeAg have a reduced ability to develop non-replicating HBV compared to HIV negative patients [21]. Reactivation can occur in immuno-compromised patients previously considered to have non-replicating infection [22].

Both the World Health Organization and the South African HIV Clinician's society recommend early screening for Hepatitis B in HIV infected patients, ideally at the time of diagnosis. Despite these recommendations, the National Department of Health guidelines no longer recommend Hepatitis B testing in HIV infected adults. Hepatitis B screening (HBsAg) was advised in the 2010 guidelines in patients starting nevirapine but only in patients with a raised Alanine Transaminase (ALT) due to toxicity concerns of administering this drug in HBV infected patients. Prior to that, screening for HBsAg was not included in the guidelines.

4.4 Co-infection treatment

The ARVs lamivudine and tenofovir are part of the first line regimen for HIV. Both are also effective treatment of HIV and HBV. Tenofovir was approved for the treatment of HBV in 2008 [17] and became available in South Africa in 2010. Lamivudine has a poor resistance profile and drug resistance mutations commonly occur after two to three years of use [23]. In addition HBV flare-ups often occur if lamivudine is stopped [24]. Tenofovir has a much better resistance profile and fewer side effects than lamivudine and is now part of first line therapy for HIV. Tenofovir can be used to treat both diseases and is often considered the preferred treatment in coinfected patients, because of this the National ART Guidelines no longer recommend screening for HBV. However, due to the lack of screening for HBV, patients are not diagnosed and their liver function tests are not being monitored.

There is no surveillance of HBV-related liver disease or adequate contact tracing to prevent the spread of HBV disease.

HBV vaccination has been available in South Africa since 1995 [8] however there is still a cohort of patients who may have acquired HBV prior to the introduction of the vaccine and who are susceptible to HBV (including the majority of patients who participated in this study).

The South African HIV Clinician's [14] society recommends:

- Screening for HBV on HIV diagnosis.
- CD4 to be taken on newly HIV diagnosed.
- ALT to be monitored on a six monthly basis.
- Vaccinating uninfected high risk individuals against Hepatitis B.
- Infants born to co-infected mothers should receive post exposure prophylaxis against HBV.
- Co-infected patients should be referred to a specialist.
- All co-infected individuals should be counselled on lifestyle modifications to reduce further liver damage – reduce alcohol intake, avoid herbal medications.

4.5 Co-infection and abnormal liver function tests

Liver function tests (LFTs) are a range of biochemical assays which indicate liver disease or damage, and elevated Aspartate Transaminase (AST) and ALT are specific biomarkers of liver damage.

Monitoring of liver function tests in co-infected HIV/HBV is important as it gives an indication of liver damage. It is of particular relevance pre starting ARVs and once initiated on ARVs as it can give an indication of hepatic flare ups.

The normal range of liver function tests are outlined below:

Table 1: Normal liver function ranges

Blood Test	Normal Range
Bilirubin	0 — 21 μmol/l
Alkaline Phosphatase	40 — 120 U/l
γ—Glutamyl Transferase (GGT)	0 — 35 U/l
Alanine Transaminase (ALT)	5 — 40 U/l
Aspartate Transaminase (AST)	5 — 40 U/l

The World Health Organization recommends that liver function tests be monitored in HIV-infected patients on a regular basis – three to six monthly. There have been very few studies in South Africa to determine the effect of co-infection on liver function. A study conducted in the Chris Hani Baragwaneth hospital in Johannesburg showed that co-infected patients had abnormal liver function tests. However, another study conducted in a South African urban clinic showed that liver function tests were not a good predictor of HBV infection [16].

5 Issues not addressed in the Literature

The gaps in the literature have been divided into the following areas:

5.1 Current co-infection prevalent HIV/HBV rates

Although there are a number of studies on HIV and HBV, there are few studies on HIV/HBV co-infection in sub-Saharan Africa. There needs to be large scale prevalence studies on co-infection within sub-Saharan Africa.

5.2 Effective treatment of co-infection in sub-Saharan Africa

There is limited data on ART treatment in co-infected patients. As both HIV and HBV are endemic in sub-Saharan Africa, this is an important area and warrants further studies.

6 Need for further research

Due to the limited data on HIV/HBV co-infection in sub-Saharan Africa and South Africa, health departments are not adequately prepared for the long term chronic effects of co-infection. As ARV programmes scale up across Africa, careful consideration needs to be given to the most appropriate treatment for co-infected individuals in places with endemic HBV rates. Currently there is no screening of patients for HBV prior to being placed on ART and thus there is very little data on whether patients are on the most appropriate ARV regimen given their co-infection status.

7 Contribution of dissertation to literature

This study will provide prevalence rates of HBV in a HIV infected population. This study will also investigate whether this cohort of patients are on appropriate anti-retroviral treatment given their co-infection status. This study will also determine whether co-infection is associated with abnormal liver function.

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PART C: MANUSCRIPT

Prevalence of Hepatitis B in HIV infected persons: Choice of antiretroviral therapy regimen and implications for screening.

1. Abstract

Background: Limited data and few studies have shown the prevalence of Hepatitis B in the HIV infected population in South Africa, whether these patients are on appropriate antiretroviral therapy and the effect of Hepatitis B on liver function in co-infected persons.

Objectives: The objectives of this study were to determine the prevalence of Hepatitis B surface antigemia (HBsAg) in healthy HIV positive persons screened for a vaccine trial and the proportion of those eligible for antiretroviral therapy that were receiving optimal anti-viral treatment, namely tenofovir and/or lamivudine. The relationship between Hepatitis B carriage and liver function was also determined in co-infected persons as measured by liver function tests.

Methods: A cross sectional study was conducted from 30th August 2011 to 24th April 2013 to determine the prevalence of HIV/HBV co-infection in persons attending a clinical trial site in an urban area of Cape Town. Participants self-presented to the clinic and once consented were enrolled into the study and provided blood for HIV confirmatory test, Hepatitis B s Ag, CD4, VL, full blood count, liver function and renal function tests.

Results: 638 participants were enrolled into this cross sectional study (85.4% female, 70.8% on ARVs). The median age was 35 years (range 18-51) with a median CD4 count of 567 10^6/l. (IQR 443-715). 24 (3.8%) were Hepatitis B s Ag positive. Of the 24 HIV/HBV co-infected participants, 19 (79.2%) were on antiretroviral therapy, 14 (73.7%) of these were on a tenofovir/lamivudine regimen the remaining 5 (26.3%) were not on a tenofovir regimen. Five of the co-infected participants were not on ARVs because their CD4 count was above the recommended South African guidelines for treatment i.e. greater than 350 10^6/l. Male participants were three times more likely to be HBsAg positive (OR 3.11, 95% CI 1.29-7.49); and elevated Alanine aminotransferase (ALT) (OR 3.306 95% CI 1.32-8.26) and Aspartate Transaminase (AST) (OR 3.18, 95% CI 1.21 – 8.34) were associated with HBsAg seropositivity. Age was not associated with the risk of HBV co-infection.

Conclusion: This study showed a lower HIV/HBV co-infection prevalence rate than reported from other locations in South Africa suggesting geographical variability. Appropriate guidelines are required to ensure that co-infected patients are identified and treated with the most appropriate anti-retroviral regimens. Also screening for HBV is recommended in HIV infected cohorts.

Key words: HIV prevalence, Hepatitis B prevalence, HIV/Hepatitis B co-infection,

Guidelines, Sub-Saharan Africa, South Africa.

2. INTRODUCTION

HIV and Hepatitis B (HBV) represent two significant global health problems. Both are preventable viral infections with increasing prevalence. Currently there are an estimated 50 million people living with HIV [1] and two billion people worldwide with Hepatitis B, with more than 240 million people living with chronic HBV [1]. Globally there is very little data on HIV/HBV co-infection. Studies from the developed world show that HBV infection is higher in HIV infected individuals compared to uninfected individuals [2]. Estimated co-infection rates in Sub-Saharan Africa are approximately 15.0% but can vary greatly between countries [3]. Co-infection prevalence rates in South Africa are currently unknown. Studies conducted in an urban clinic in Johannesburg estimated a 5.0% HBsAg positivity rate in HIV positive patients compared to 17.0 % in an industrial clinic setting [4]. South Africa has one of the highest HIV prevalence rates in the world, with an estimated 10.6% of the population infected with HIV in 2011 [5]. There has been a strong drive within the last few years to increase screening rates for HIV and to provide HIV positive people with appropriate medical care, however HBV screening is not conducted in South Africa and the current co-infected prevalence rates are unknown.

The current standard of care against HBV is vaccination at birth which has been implemented since 1995 [6]. People who test HIV positive are monitored routinely and initiated on ARVs once their CD4 count is below 350 x 10^6/L. Tenofovir has been part of the first line treatment for HIV in South Africa since 2010 and lamivudine since 2004, both of these drugs are effective in the management of HBV. Lamivudine has a poor resistance profile and drug resistance mutations commonly occur after two to three years of use [7]. In addition HBV flare-ups often occur if lamivudine is stopped [7]. Tenofovir has a much better resistance profile and fewer side effects than lamivudine. Tenofovir can be used to treat both diseases

and because of this the National ART Guidelines no longer recommend screening for HBV. Many co-infected patients initiated on ART prior to 2010 may not be on tenofovir.

Currently the Southern African HIV Clinicians Society recommends screening for HBV on initial diagnosis of HIV. However, in the 2010 Department of Health HIV management guidelines, stavudine has been replaced with tenofovir and screening for HBV is no longer required. The proportion of co-infected positive persons on appropriate antiretroviral treatment is not known. The purpose of this study is to evaluate the prevalence of HIV/HBV co-infection and the number of persons on appropriate anti-retroviral treatment.

3. METHODS

3.1 Setting and population

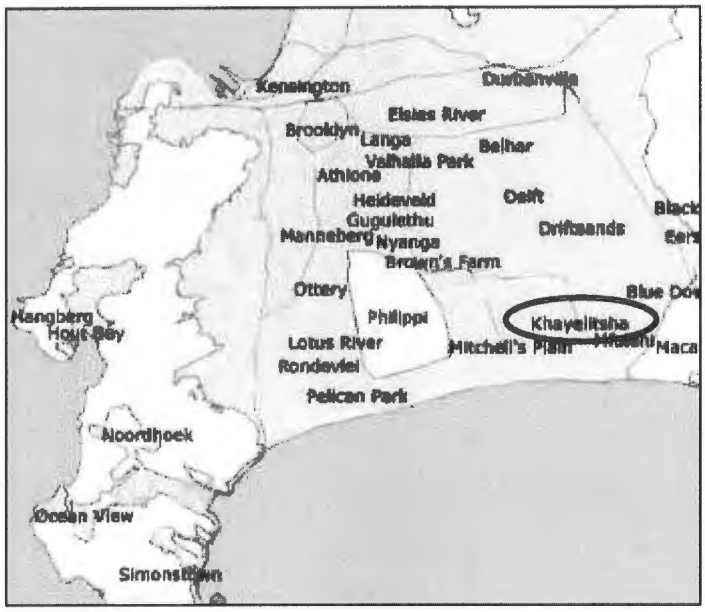
This study was part of a TB vaccine trial conducted in an urban clinic in Khayelitsha, Cape Town. Participants were recruited from surrounding township clinics and self-presented to the clinic for enrolment into the study. Radio and newspaper adverts were also used as a recruitment tool.

Participants were recruited from 30th August 2011 to 24th April 2013. As part of the TB vaccine trial, participants signed a full informed consent, had a complete TB screen conducted and bloods taken for confirmation of HIV status, Hepatitis B screening, CD4, HIV viral load and liver profile.

Participants were HIV-infected males and females aged 18 to 51 years old, who had no current signs or symptoms of tuberculosis at the initial assessment, their most recent CD4 result was greater than 300 x 10^6/L if on ARVs and if ARV naïve greater than 350 x 10^6/L. Pregnant women were excluded. A total of six hundred and ninety six participants consented for the TB vaccine trial; six hundred and thirty eight participants had bloods taken and were included in this cross sectional prevalence study.

Khayelitsha is an urban township in Cape Town comprising of formal and informal housing. Adults aged 15-54 years of age comprise of 66.7 % of the population. Half of all adults are unemployed and of those employed, 80% earn less than R1600 per month [8].

Figure 1: Cape Town with Khayelitsha



[9]

3.2 Study design and collection

All data was collected by the TB vaccine trial. Trained research field workers and professional nurses obtained the demographic information and professional nurses collected blood samples.

3.3 Data analysis

All data were double entered in EXCEL and then cross referenced to ensure consistency. Stata version 12 (Stata Corp. LP, College Station, TX, United States of America) was used for all analyses. Descriptive statistics were conducted calculating means, standard deviations for normally distributed data and mean and interquartile ranges used for data not normally distributed. Odds ratios were used to identify measures of association between HBV status and variables such as sex. Logistic regression was used to explore factors associated with HBV/HIV co-infection. Significantly associated risk factors that were identified were then introduced into a respective multivariable model with variables being retained in the final model if associated likelihood ratio test showed a P value of <0.05.

4. Ethical Considerations

All participants signed informed consent prior to participating in the vaccine trial (REC REF: 001/2010). This study was granted full ethics approval by the University of Cape Town Human Research Ethics Committee (HREC REF: 305/2013).

5. RESULTS

5.1 Demographic Data

A total of 638 participants were included in this cross sectional study and the majority were female (n=545, 85.4 %,). The median age was 34.6 years (range 18-51).

31% (n=197) of participants lived in a house or formal building, 33.4% (n=213) lived in informal dwellings with sanitation and the remainder 35.7% (n=228) lived in informal dwelling without sanitation but had access to a communal toilet.

The overall prevalence rate of HBV was 3.8% (n=24). Over seventy percent (n=447) of all participants were on anti-retrovirals. The majority of women (78.3 % n= 426) described themselves as non-drinkers whereas more than half of the men (52.7% n=49) consumed alcohol.

There was a higher proportion of men co-infected (8.6% n=8) compared to women (2.9% n=16).

Table 1 presents the demographic information and HBV, ARV status categorized by gender.

Table 1: Demographic data, HBV and ARV status of participants in study

Variables	Female	Male	Total	P value	Odds Ratio	CI OR
% Total	545 (85.4%)	93 (14.6%)	638 (100.0%)			
Mean Age	34.1; SD(6.9)	37.4; SD (6.1)	34.6; SD (6.8)	<0.001		95% CI of the difference -4.76 to -1.78
On ARVs	384 (70.8%)	63 (67.7%)	447 (70.4%)	0.544,	0.864	0.539, 1.386
Not on ARVs	158 (29.2%)	30 (32.3%)	188 (29.6%)			
Hep B s Ag positive	16 (2.9%)	8 (8.6%)	24 (3.8%)	0.015f,	3.112	1.292, 7.495
Hep B s Ag negative	529 (97.1%)	85 (91.4%)	614 (96.2%)			
Drinker	118 (21.7%)	44 (47.3%)	162 (25.4%)	<0.001,	0.308	0.196, 0.486
Non Drinker	426 (78.3%)	49 (52.7%)	475 (74.6%)			
Type of accommodation						
Formal building	167 (30.6%)	30 (32.3%)	197 (30.9%)	0.325	N/A	N/A
Informal building with sanitation	188 (34.5%)	25 (26.9%)	213 (33.4%)			
Informal building with communal sanitation	190 (34.9%)	38 (40.9%)	228 (35.7%)			

f= fisher's exact test

5.2 CD4 counts and Viral Loads

The median CD4 count of the cohort was 567 x 10^6/l (IQR 447-716 x 10^6/l). Overall, 70.4% of the cohort (n=447) were on anti-retrovirals of whom 23.3% (n=55) had a detectable viral load.

5.3 Co-infection and ARVs

24 participants were co-infected, 5 of whom were ARV naïve as their CD4 count did not meet the eligibility criteria for initiating therapy according to the South African guidelines. The remaining 19 participants (79.1%) were on ARVs of whom 14 (73.7%) were on a tenofovir/lamivudine based regimen, and 5 (26.3%) were on a lamivudine containing regimen without tenofovir.

5.4 Liver function test

Table 2 presents the features of the co-infected participants and those who were not Hepatitis B infected within the cohort. A greater proportion of men than women were co-infected, men were three times more likely to be HBsAg positive. 9.3% (n=7) of the HIV/HBV co-infected cohort had abnormal ALTs and 9.4% (n=6) of co-infected participants had abnormal AST results.

Table 2: Hepatitis B prevalence

Variable	Hep B s Ag negative (N=614)	Hep B Ag positive (N=24)	Total	P value, unadjusted	Odds Ratio	CI of OR
Males	85 (91.4%)	8 (8.6%)	93 (100.0%)		3.112	1.292, 7.495
Females	529 (97.1%)	16 (2.9%)	545 (100.0%)	0.015f,		
Age mean (SD)	34.54 (6.64)	36.25(6.76)		0.231		-1.09 to 4.50
On ARVs	428 (95.7%)	19 (4.3%)	447 (100%)		1.625	0.598, 4.418
Not on ARVs	183 (97.3%)	5 (2.7%)	188 (100.0%)	0.921,		
Drinker	157 (96.9%)	5 (3.1%)	162 (100%)		1.308	0.481, 3.562
Non-drinker	456 (96.0%)	19 (4.0%)	476 (100%)	0.598,		
ALT abnormal (if >40 U/l)	68 (90.7%)	7 (9.3%)	75 (100%)		3.306	1.323, 8.260
ALT normal (if <=40 U/l)	546 (97.0%)	17 (3.0%)	563 (100%)	0.016f,		
AST abnormal (if > 40 U/l)	58 (90.6%)	6 (9.4%)	64 (100%)		3.184	1.216, 8.338
AST normal (if <= 40 U/l)	554 (96.9%)	18 (3.1%)	572 (100%)	0.026f,		
AP abnormal (if >120 U/l)	64 (95.5%)	3 (4.5%)	67 (100%)		1.223	0.355, 4.215
AP normal (if <=120 U/l)	548 (96.3%)	21 (3.7%)	569 (100%)	0.732f,		
GGT abnormal (if >35 U/l)	302 (95.0%)	16 (5%)	318 (100%)		2.060	0.869, 4.883
GGT normal (if <=35 U/l)	311 (97.5%)	8 (2.5%)	319 (100%)	0.094,		
Bilirubin abnormal (if > 21 µmol/l)	3 (75%)	1 (25%)	4 (100%)		8.855	0.887, 88.423
Bilirubin normal (if <= 21 µmol/l)	611 (96.4%)	23 (3.6%)	634 (100%)	0.143f,		
Platelets abnormal (if > 400 x 10^9/l)	61 (98.4)	1 (1.6%)	62 (100%)		0.394	0.052, 2.970
Platelets normal (if <= 400 x 10^9/l)	553 (96.0%)	23 (4.0%)	576 (100%)	0.499f,		
For those on ARVs VL abnormal >40	38 (86.4%)	6 (13.6%)	44 (100%)		4.591	1.650, 12.773
For those on ARVs VL normal <=40 or LDL	378 (96.7%)	13 (3.3%)	391 (100%)	0.008f,		

f= fisher's exact test

5.5 Impact of co-infection on liver function

Co-infected participants were 3.3 times more likely to have abnormal ALT results and 3.5 times more likely to have abnormal AST results in this prevalence study. These results were statistically significant.

Table 3: Impact of co-infection on bloods

Variables	P value	Confidence Interval	Adjusted OR
ALT	0.010	1.323, 8.260	3.337
AST	0.018	1.216, 8.338	3.486
AP	0.750	0.355, 4.215	1.050
GGT	0.101	0.869, 4.883	1.911
Bilirubin	0.063	0.887, 88.423	10.761
Platelets	0.366	0.052, 2.970	0.390
* adjusted for age/gender/ARVs/Alcohol			

6. Discussion

This study of 638 healthy HIV-infected participants from Khayelitsha included a high proportion of women reflecting the predominance of women attending HIV services in the public sector and volunteering for studies. South African women have had an earlier exposure to HIV services through MTCT prevention programs and many cohorts reflect this gender imbalance [10]. The overall prevalence of 3.8% HBV/HIV co-infection rates in our study was lower than expected when compared to other studies [4]. Previous prevalence studies on HBV mono-infection conducted in South Africa, reveal varying results from 1 % in urban areas to up to 10 % in rural areas [4]; [2]. Two different studies conducted in Johannesburg HIV clinics with a similar median age to this study showed a 5% prevalence of co-infection in a government ARV clinic [11], [4]. HIV programs in an industrial mining setting revealed 20 % of their total cohort (predominantly men) were co-infected [12]. The lower prevalence rate in our study may be due to the fact that this population were healthier and had higher CD4 counts compared to previous studies [13]. It may also be due to the low proportion of

men aware of their HIV status and attending services and recruited into this study, as men have a higher prevalence of HBsAg carriage compared to women [6]. The low prevalence of co-infection was surprising as a large proportion of residents of Khayelitsha have recently migrated from the Eastern Cape [14] and studies show that the prevalence of Hepatitis B is much higher in communities in the Eastern Cape [6].

This study revealed that co-infected participants were 3.3 times more likely to have some degree of liver inflammation as indicated by an abnormal ALT and AST results compared to mono HIV infected participants. However, other studies have produced conflicting reports regarding impaired liver function tests and co-infection. ALT levels tend to be lower or within normal ranges within co-infected patients [11] however, significant fibrosis can still be present [15].

Further studies have shown elevated liver function tests in the majority of AIDS patients who were co-infected [16],[13]. In contrast, one of the studies conducted in Johannesburg showed that liver function tests were not an adequate marker of HBV infection as ALT results were often normal in co-infected patients [4].

Our study shows a correlation between raised ALT and AST and co-infection, however this result should be viewed with caution as the majority of these patients were on ARVs. ALT levels can fluctuate in co-infected patients for many reasons such as effects of antiretrovirals, alcohol consumption and immune reconstitution [15]. Also intermittent ALT elevations can be seen during hepatic flare ups [15]. Raised HBV DNA levels are a more accurate measure of liver damage [15] but this test was not conducted as part of this study.

Of the 24 HIV/HBV co-infected participants, 19 (79.2%) were on antiretroviral therapy, 14 (73.7%) of these were on a tenofovir/lamivudine regimen and the remaining 5 (26.3%) were not on the recommended tenofovir regimen. The inappropriate ARV choice may be a result

of lack of screening for HBV. Five of the co-infected participants were not on ARVs because their CD4 count was above the recommended South African guidelines for treatment i.e. greater than 350 x 10^6/l. Although, the numbers of HBV positive individuals in this study are small, it indicates the need for HBV screening in all HIV diagnosed patients and to ensure that co-infected patients are on appropriate treatment. Appropriate medical follow-up for co-infected patients is also necessary. However, this has not been included in the national guidelines although recommended by the South African Clinician's Society.

Possible limitations to this study were low recruitment numbers for the sub analysis of the co-infected group and a disproportionate low number of males recruited into the study which could account for the low prevalence rates. Also, this cohort of patients were healthy HIV infected adults with high CD4 counts and were proactively engaged in their health care management. Limited Hepatitis B testing was conducted; HBsAg was the only test conducted, other markers such as Hepatitis B e Ag or HBV DNA were not conducted which can give a better indication of liver damage in co-infected patients. Overall, the estimate for the proportion of co-infected persons in our sample was 24 (95% CI 1.3 to 7.5) and therefore we cannot generalise to other populations with accuracy.

7. Conclusion

Screening for HBV is recommended by both the World Health Organization and the South African HIV Clinician's Society. This is not being routinely conducted in South Africa. Given the varying co-infection estimation rates throughout the country routine HBV screening is required to accurately estimate rates of co-infection. However this would have cost and logistical implications which may be impractical given the current demand on the South African healthcare system. A more practical recommendation may be to initiate HBV screening in patients with raised LFTs

The rate of HIV/Hep B co-infection was lower than expected within this cohort but this may have been due to the predominance of women and the fact that participants in a trial were more likely to be healthy with higher median CD4 counts. Despite improvements in ARV treatment guidelines and the introduction of tenofovir as first line treatment, this study revealed that co-infected participants are on inappropriate ARVs. This warrants further investigation.

8. Acknowledgements

I would like to thank the staff of the eKhayavac Clinic at Khayelitsha and the staff of the IIDMM at the University of Cape Town.

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Amendment Form

Date	06 Nov 2012
HREC REF Number	001/2010
Protocol number (if applicable) & Protocol title	A Phase 2, Proof of Concept, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Protective Efficacy Against TB Disease, Safety and Immunogenicity of MVA85A/AERAS in Healthy HIV infected Adults
Principal Investigator	Professor Robert Wilkinson
Department / Office Internal Mail Address	Room 3.03 Wolfson Pavillion, Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of cape Town, Anzio Road, Observatory, 7925.

List of Proposed Amendments with Revised Version Numbers and Dates

1. Please note that the back translated Xhosa informed consent form was incorrect.
2. Attached the summary of missing information, all participants who were consented on version 8.0 will be re-consented on this summary page (attached).
3. English Informed consent form version 8.0 remains unchanged
4. Xhosa informed consent updated to version 8.1 to include missing information

HUMAN RESEARCH
ETHICS COMMITTEE
- 7 NOV 2012
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

HREC office use only (FWA00001637; IRB00001938)

☑ Approved	☑ Type of review: Expedited	☐ Full committee

This serves as notification that all changes and documentation described above are approved.

Signature Chairperson of the HREC		Date	8/11/2012 8/11/2012

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
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www.health.uct.ac.za/research/humanethics/forms

27 May 2013

HREC REF: 305/2013

Ms D Reidy
15 Hely Hutchinson
Camps Bay
Cape Town 8005

Dear Ms Reidy

PROJECT TITLE: PREVALENCE OF HEPATITIS B IN HIV INFECTED PERSONS: CHOICE OF ANTIRETROVIRAL THERAPY REGIMEN AND IMPLICATIONS FOR SCREENING

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year till the 28 May 2014.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

pp **PROFESSOR M BLOCKMAN**
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

sAriefdien

Apendix 1: Inclusion/Exclusion Criteria to TB Vaccine Trial

Inclusion Criteria

Subjects must meet <u>all</u> of the following criteria at the time of randomization:

1. Has completed the written informed consent process prior to undergoing any screening evaluations.
2. Either males or females aged ≥18 and ≤50 years on Study Day 0
3. In general good health, confirmed by medical history and physical examination
4. Has ability to complete follow-up period as required by the protocol
5. Has laboratory evidence of human immunodeficiency virus (HIV) infection, defined as a positive HIV-1 ELISA test plus a positive confirmatory test (e.g., a second HIV-1 ELISA, PCR, or rapid ELISA) diagnosed prior to randomization
6. Is willing to allow the investigators to discuss the subject's medical history with the subject's HIV physician
7. If not receiving ART at the time of randomization, must have 2 CD4+ lymphocyte count test results >350 cells/mm^3, performed at least 4 weeks apart, one performed within 6 months prior to randomization and one within 45 days prior to randomization
8. If receiving antiretroviral therapies (ART) at the time of randomization, must have 2 CD4+ lymphocyte count test results >300 cells/mm^3, performed at least 4 weeks apart, one performed within 6 months prior to randomization and one within 45 days prior to randomization
    a. Subjects on ART must have been receiving ART for at least 6 months prior to randomization and must have an undetectable HIV viral load within 45 days prior to randomization
    b. Women who received ART as part of the PMTCT program must have completed therapy at least 2 months prior to randomization
9. Has either
    a. a negative QuantiFERON-TB Gold In-Tube test result and tuberculin PPD skin test ≤5 mm induration within 45 days prior to randomization or
    b. a positive QuantiFERON-TB Gold In-Tube test result and/or tuberculin PPD skin test >5 mm and has completed at least 5 months of isoniazid preventive therapy within 3 years prior to randomization or
    c. a positive QuantiFERON-TB Gold In-Tube test result and/or tuberculin PPD skin test >5 mm and has completed treatment for TB disease within 3 years prior to randomization
10. Females: Ability to avoid pregnancy during the trial. Women physically capable of pregnancy (not sterilized and still menstruating or within 1 year of the last menses if menopausal) in sexual relationships with men must avoid pregnancy by using an acceptable method of avoiding pregnancy from 28 days prior to administration of the study vaccine through 6 months after the last study vaccination. Acceptable methods of avoiding pregnancy include a sterile sexual partner, sexual abstinence (not engaging in sexual intercourse), and any contraceptive method deemed clinically suitable by the trial clinician taking into account ART status.
11. Has completed the written informed consent process for simultaneous enrollment in Aeras Vaccine Development Registry protocol

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